REMARKS

Claims 1, 3-13, 28-36, 38-47, 62 and 63 were pending in the Application at the time of December 3, 2002 Official Action. While not necessarily in agreement with the rejections made by the Examiner, Applicants have amended the claims to expedite review and allowance. Specifically, claims 1, 28, 30, 32, 34, 36, and 38 have been amended. No new matter has been added to the Application by way of any of the amendments to the claims. Applicants reserve the right to prosecute any cancelled claim matter in later applications.

Withdrawn Rejections

Applicants thank the Examiner for withdrawing the rejection of claims 9, 28-35, 44 and 64 under 35 USC 112, second paragraph. Applicants also thank the Examiner for removing the rejection of claims 36-38 under 35 USC 102(b).

Rejection of Claims 28-35 and 38-44 under 35 USC § 112, First Paragraph

The Examiner has rejected claims 28-35 and 38-44 under 35 USC § 112, first paragraph as "containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention."

Specifically, the Examiner rejected claims 28, 30, 32, and 34, stating that claims 28, 30, 32 and 34 are drawn to a method for treating...administering...a compound of claim 1', however, claim 1 is also drawn to "a method of" treating" and not to a compound. Therefore, the claims, as amended, are improperly dependent on claim 1 because the claims are drawn to different methods."

While not necessarily agreeing with the Examiner, Applicants have amended claims 28, 30, 32 and 34 to expedite review and allowance, while reserving the right to prosecute cancelled subject matter in later applications.

The Examiner also rejected claim 38 because it improperly depended from cancelled claim 37.

Applicants have amended claim 38 to depend on claim 36, thereby providing dependency from a currently pending claim.

No new matter was added by way of these amendments.

Applicants respectfully request that the Examiner reconsider the 112, first paragraph, rejection of claims 28-35 and 38-44 in view of the amendments accompanying this response.

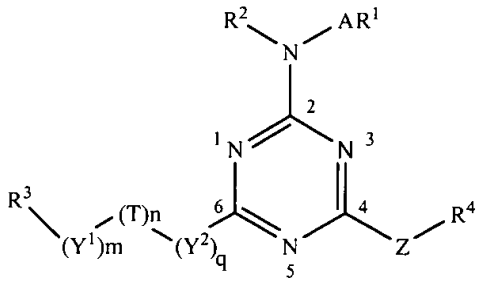
Rejection of Claims 1, 28-35, 36 and 62-63 under 35 USC § 102(a)

The Examiner rejected claims 1, 28-35, 36 and 62-63 under 35 USC § 102 (a) in view of Moriarty et al., WO 01/47897, stating:

> " The instantly claimed compounds and the methods of use read on the reference disclosed compounds and the use thereof. See formula I in page 3 and the use of the compounds in pages 14-16 wherein the compounds are disclosed to be useful in the treatment of atherosclerosis. The instant claims read on the prior art taught therapeutic effect because the instant claims are drawn to administration of the prior art compounds, in same dosages, to same population. The therapeutic effect of claim 1 is evident from page 2 of the specification and the therapeutic effects of claims 28, 30, 32 and 34 is evident from the respective dependent claims. The prior art also teaches that the compounds are useful in the treatment of the instantly claimed disease, namely atherosclerosis (see page 16, line 5) and therefore, the instantly claimed mechanism of sodium channel modulation is inherently taught in the reference."

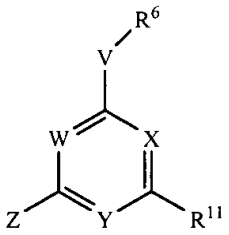
The Examiner has also asserted that the subject application "can not rely on the benefit of priority based on Provisional Application 60/251,916 (filed December 7, 2000)". Applicants do not agree with the Examiner's assessment, but in an effort to move this application along to allowance, present the following arguments over WO 01/47897.

The generic formula of the subject application is shown below:

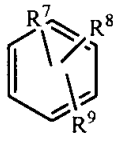


Formula 1

WO 01/47897 (Moriarty) discloses the following structure:



where the R^6 substitutent is defined as:



In the compounds of WO 01/47897 R^6 must always be a substituted phenyl. The compounds in WO 01/47897 are named as 2yl-amino-4-methylbenzamides (for example see bottom of page 72) or 2-ylmethyl-4-methylbenzamides (for example, see the top of page 30).

If one looks at the substituent choices at the 2-position of the present invention, one will see that A can be $-C(Z^1)-$, $-C(Z^1)-NH-$, SO_2, or a covalent bond. The only choices that are even close to those shown in WO 01/47897 would be when A equals a covalent bond. Even if A is chosen to be a covalent bond, then the R^1 substituent in the present invention would have to be a substituted phenyl to even begin to have WO 01/47897 be a 102(b) reference. In addition, to be a 102(b) reference, the 4- and 6-position substituents of WO 01/47897 would have to be chosen to match the present invention. To accomplish such matching would require using hindsight – looking at the present invention and finding similarities among the thousands of compounds in WO 01/47897,

While not in agreement with the rejection made by the Examiner, Applicants, in an attempt to move this application toward allowance, have amended claim 36. The amendment eliminates the possibility that R^1, of the subject invention, which is the equivalent of R^6 of Moriarty, can be substituted phenyl. Applicants reserve the right to prosecute the cancelled subject matter in later applications.

The Examiner has rejected claim 1 on the basis of WO 01/47897, saying that "[t]he therapeutic effect of claim 1 is evident from page 2 of the specification". Applicants have reviewed page 2 of WO 01/47897 and respectfully point out that there page 2 of WO 01/47897 does not point out "an agent capable of increasing ABCA-1 expression". On page 2 of WO 01/47897 there is a discussion of the forms of p38, two of which are thought to be key mediators of TNF-α production. Page 3 WO 01/47897 goes on to state that the "compounds of the present invention are useful in the treatment of p38- and TNF-α expression-mediated inflammatory and other disorders". Among the "other disorders" atherosclerosis is listed.

The present invention is directed to reducing the risk of formation of atherosclorotic plaques in arteries by reducing plasma lipid levels. One of the methods is efflux of cholesterol from cells by active transfer to apolipoprotein A-1. Transfer to apolipoprotein A-1 is mediated by a protein known as ATP binding cassette transporter 1 (ABC-1, or alternatively referenced as ABCA-1).

TNF-α (or tumor necrosis factor) is a cytokine with many actions, including the mediation of inflammatory responses through its vasodilatory effects, stimulation of tumor cell proliferation accompanied by a cytotoxic action, stimulation of T-cell mediated immunity to tumor cells, and an ill-defined action leading to wasting in cancer patients. TNF binds to two distinct cell surface receptors, one expressed on a wide variety of cells, the other expressed primarily on lymphoid and myeloid cells. TNF-α is produced by macrophages, eosinophils and natural killer cells and is encoded by a gene on human chromosome 6p23. The mature protein of 157 amino acids has an M_r of 17,000 and has no potential gycosylation sites, but does possess cysteine residues capable of forming disulphide bonds.

ATP-binding cassette proteins (ABC proteins) are a family of transport proteins all containing a structurally similar ATP-binding domain of ~200 amino acids containing two short ATP-binding motifs.

From these two short descriptions, it can be seen that TNF-α and ABCA-1 activities are not caused by the same mechanisms. Applicants respectfully point out that the Examiner has used hindsight to make this rejection of claim 1. There is no discussion of ABCA-1 in WO 01/47897 and being able to increase ABCA-1 expression is required in claim 1 of the present application. Applicants ask the Examiner to explain how inhibition of TNF-α activity is the

same as increase in ABCA-1 expression. For this reason, Applicants respectfully request the Examiner to reconsider the 35 USC §102(a) rejection of claim 1.

The Examiner has rejected claims 28-31 on the basis of WO 01/47897. Applicants respectfully point out that independent claim 28 is directed to a method for raising HDL cholesterol. Dependent claims 29-31 contain all of the limitations of independent claim 28.

The Examiner has rejected claims 32-33 on the basis of WO 01/47897. Applicants respectfully point out that independent claim 32 and dependent claim 33 are directed to methods for promoting cholesterol efflux from cells.

The Examiner has rejected claims 34-35 on the basis of WO 01/47897. Applicants respectfully point out that claim 34 is directed to methods of treating coronary artery disease with a combination of a compound that elevates serum levels of HDL cholesterol and a compound that lowers LDL cholesterol. Claim 35 is dependent on claim 34 and contains all of the limitations of independent claim 34.

The Examiner has pointed to "the respective dependent claims" as teaching the same therapeutic effect as claims 28, 30, 32 and 34. Applicants have reviewed the dependent claims in WO 01/47897 and respectfully point out to the Examiner that they cannot find any reference to raising HDL cholesterol, lowering LDL cholesterol, or a combination therapy directed to the same features. Applicants request the Examiner to clarify the rejection of claims 28, 30, 32, and 34.

The Examiner has also rejected claims 62 and 63 as being anticipated by WO 01/47897. Applicants request the Examiner to review the above arguments. The compounds of the present invention are not anticipated by the compounds of WO 01/47897. Therefore, a pharmaceutical composition utilizing the compounds of the present invention should not be anticipated by a pharmaceutical composition for different compounds. For this reason, Applicants request the Examiner to reconsider the 35 USC §102(a) rejection of claims 62 and 63.

Applicants ask the Examiner to reconsider the rejection of claims 1, 28-35, 36 and 62-63 under 35 USC § 102(a) in view of WO 01/47897 (Moriarty) and to withdraw the rejection.

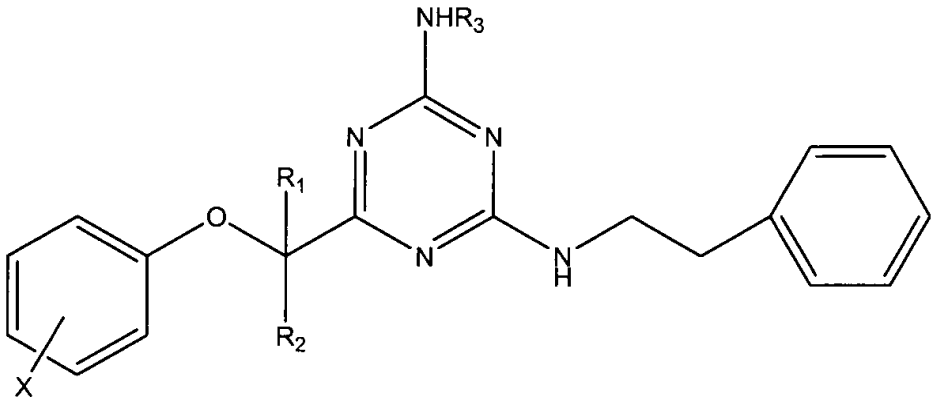
Applicants also ask the Examiner to explain the last sentence in the 35 USC §102(a) section of the Office Action (just above the note on page 4). This sentence reads in part "and therefore, the instantly claimed mechanism of sodium channel modulation is inherently taught in

the reference". Applicants are unaware of any discussion of sodium channel modulation in either the present invention or WO 01/47897.

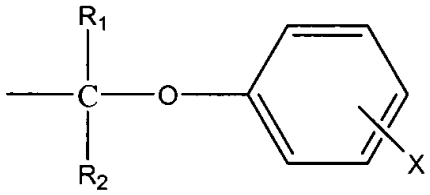
Rejection of Claims under 35 USC § 102(b)

1. The Examiner rejected claims 1 and 28-35 under 35 USC § 102(b) in view of GB 1,384,684.

Applicants respectfully traverse the rejection. To anticipate a claim, a single reference must contain all the elements of that claim. The compound discussed in the GB patent is shown below (drawn in a manner similar to the compounds of the present application).



GB 1,384,684 requires that the substituent in the 6-position be carbon attached to an oxygen atom, which is, in turn, attached to a substituted phenyl. This is shown as

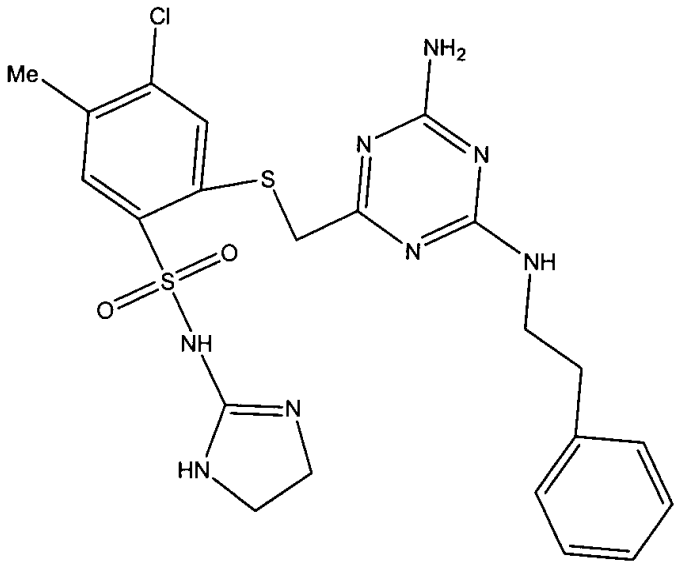


While not necessarily agreeing with the Examiner's rejection of claim 1 based on GB 1,384,684, Applicants, in an attempt to move this application toward allowance, have amended claims 1, 28, 30, 32, and 34. As dependent claims, claims 29, 31, 33, and 35 carry all of the limitations of the claims upon which they are dependent. Applicants reserve the right to prosecute any cancelled subject matter in later applications.

Applicants respectfully request that the Examiner reconsider the rejection of claims 1 and 28-35 under 35 USC 102(b) as being anticipated by GB 1,384,684.

2. The Examiner has rejected claim 36 under 35 USC § 102(b) as being anticipated by Kozakiewicz Chem. Abstract 130:267406 (1999). The Examiner specifically mentioned RN 222418-76-0.

The Kozakiewicz compound has the following structure (when drawn in a manner similar to the compounds of the present invention).

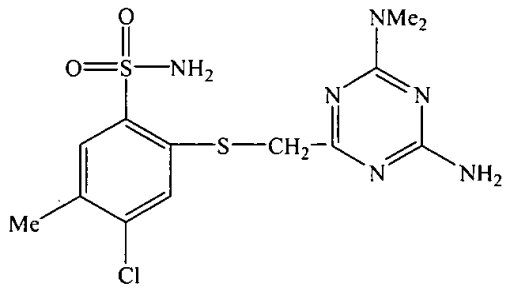


Kozakiewicz names his compound 2-[[[4-amino-6-[(2-phenylethyl)amino]-1,3,5-triazin-2-yl]methyl]thio]-4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-5-methyl-benzenesulfonamide. Thus, Kosakiewicz requires an amino group attached to the 2-position carbon, an -NH group bound to the carbon in the 4- position, and a methylene bound to the carbon at the 6-position.

While not necessarily in agreement with the rejection made by the Examiner Applicants have amended claim 36 to move this application toward allowance. Applicants reserve the right to prosecute any cancelled matter in later applications.

Applicants request the Examiner to reconsider the rejection of claim 36 under USC § 102(b).

3. The Examiner rejected claims 36 and 63 under USC § 102(b) as being anticipated by the compounds of Pomarnaka et al. Chem. Abstract 130:153642 (1998), especially RN 201229-87-0. This compound is shown below:



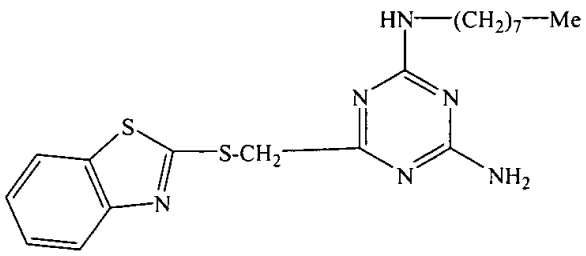
The compound of Pomarnaka the Examiner pointed out requires an amino group attached to the 2-position carbon, an -NH group bound to the carbon in the 4- position, and an ethylene bound to the carbon at the 6-position.

While not necessarily in agreement with the rejection made by the Examiner Applicants have amended claim 36 to try to move this application toward allowance. Applicants reserve the right to prosecute cancelled matter in later applications.

The Examiner rejected claim 63 under 35 USC §102(b) as being anticipated by Pomarnacka. Applicants respectfully point out that claim 63 is dependent upon claim 36 and thus contains all of the limitations of claim 36.

Applicants respectfully request that the Examiner reconsider the rejection of claims 36 and 63 under 35 USC § 102(b) as being anticipated by Pomarnacka

4. The Examiner has rejected claim 36 under USC § 102(b) as being anticipated by Kelarev et al. Chem. Abstract 130:68841 (1998), especially RN 213697-64-4. The compound shown in Kelarev is shown below:

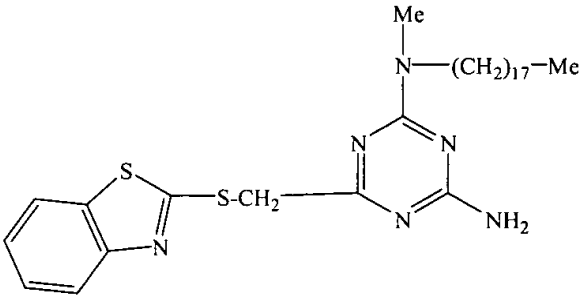


The compound of Kelerev requires an amino group attached to the 2-position carbon, an -NH group bound to the carbon in the 4- position, and a methylene bound to the carbon at the 6-position.

While not necessarily in agreement with the Rejection made by the Examiner Applicants have amended claim 36 in an attempt to move this application toward allowance. Applicants reserve the right to prosecute cancelled matter in later applications.

Applicants respectfully request that the Examiner reconsider the rejection of claim 36 under 35 USC 102(b) as being anticipated by Kelerev

5. The Examiner rejected claim 36 under USC § 102(b) as being anticipated by Silin et al., Chem. Abstract 129:260428 (1998), especially RN 213697-59-7. This compound is shown below:



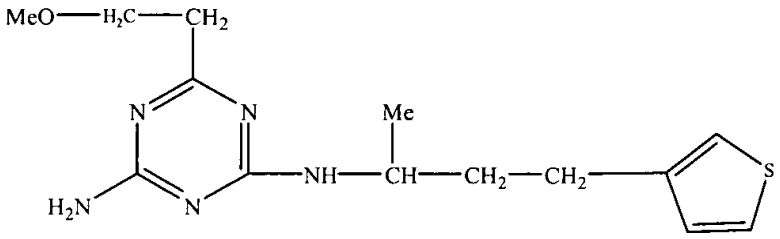
Compound 213697-59-7

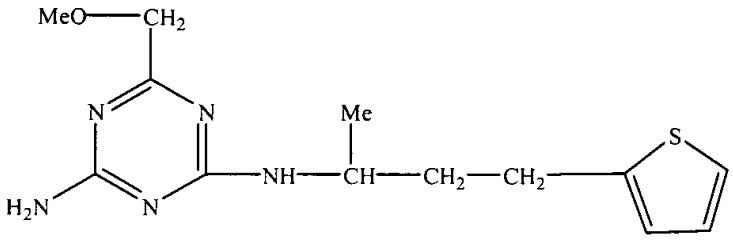
The compounds of Silin require an amino group attached to the 2-position carbon, an -NH group bound to the carbon in the 4- position, and an ethylene bound to the carbon at the 6-position.

While not necessarily in agreement with the rejection made by the Examiner Applicants have amended claim 36 to move this application along toward allowance.

Applicants respectfully request the Examiner to reconsider the rejection of claim 36 under 35 USC 102(b) as being anticipated by Silin

6. The Examiner rejected claim 36 under USC § 102(b) as being anticipated by Dollinger et al., Chem. Abstract 128:270618 (1998), especially compounds RN 205532-34-9 and 205532-38-3. The compounds in Dollinger are shown below:





Dollinger requires an amino group attached to the 2-position carbon, an -NH group bound to the carbon in the 4- position, and a methylene bound to the carbon at the 6-position.

While not necessarily in agreement with the rejection made by the Examiner, Applicants have amended claim 36 in an attempt to move this application toward allowance.

Applicants request the Examiner to reconsider his rejection of claim 36 under USC § 102(b).

General Comments in the Office Action

Some of the amendments of the claims were to correct spacing and punctuation errors. For example, claims 1 and 36 were amended correct the spacing to make the definition of the R^5 substituents of Formula I clearer.

Applicants do not believe that any of the amendments to the above claims raise any new matter issues and ask that the examiner enter these amendments.

Allowable Subject Matter

The Examiner has objected to claims 3-13 as being dependent upon a rejected base claim, but has stated that these claims would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicants believe that amended claim 1 is patentable, and respectfully request the Examiner to reconsider the objections to claims 3-13.

The Examiner has objected to claims 38-44, stating that these claims would be allowable if rewritten to overcome the rejections(s) under 35 U.S.C. § 112, second paragraph, set forth in this Office action and to include all the limitations of the base claim and any intervening claim.

Applicants believe that amended claim 38 is patentable, and respectfully request the Examiner to reconsider the objections to claims 38-44.

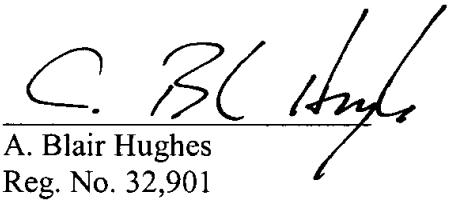
Conclusion

Claims 1, 3-13, 28-36, 38-47, 62 and 63 are pending as a result of this Reply. In view of the above amendments and arguments, Applicants believe that all of pending claims 1, 3-13, 28-36, 38-47, 62 and 63 are allowable. Applicants request the Examiner to reconsider the rejections set forth in this Office Action in view of the above arguments and claim amendments. Favorable reconsideration and allowance of the pending application claims is therefore courteously solicited.

Respectfully submitted,

McDonnell Boehnen Hulbert & Berghoff

Dated: May 29, 2003

By: 

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